CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76075

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-075 SPONSOR : Altana, Inc.

DRUG AND DOSAGE FORM : Econazole Nitrate Cream

STRENGTH(S) : 1%

TYPES OF STUDIES : Clinical endpoint bioequivalence study

DSI INSPECTION STATUS

Inspection needed: **NO**	Inspection status:	Inspection results:
First Generic ____	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
Other ____		

ASSOCIATE DIRECTOR FOR MEDICAL AFFAIRS: DENA R. HIXON, M.D.

INITIAL : DRH DATE : 9-13-02

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 9/13/02

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-075 APPLICANT: Altana, Inc.

DRUG PRODUCT: Econazole Nitrate Cream, 1%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Using definitions of clinical, mycological, and therapeutic cure that incorporates results at both 4 weeks (end of treatment) and 6 weeks (2 weeks post-treatment follow up), the study submitted is adequate to demonstrate bioequivalence.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 19 2002

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-075 APPLICANT: Altana, Inc.

DRUG PRODUCT: Econazole Nitrate Cream, 1%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your original analysis using the correct clinical cure definition fails to demonstrate bioequivalence between your product, Econazole Nitrate Cream, 1%, and the reference listed drug (RLD), Spectazole® (Ortho McNeil Pharmaceuticals) in the treatment of tinea pedis.

2. The primary endpoints for bioequivalence studies with clinical endpoints have been carefully selected in consultation with the appropriate new drug division. These are not always the same endpoints as those that are used to evaluate efficacy of a new drug product. Please refer to the "1990 Draft Guidance for the Performance of a Bioequivalence Study for Topical Antifungal Products". This guidance was prepared by the Office of Generic Drugs with consultation from the CDER division responsible for topical antifungal drug products. In discussing the primary endpoints, the guidance states: "While these comparisons should be evaluated at the end of treatment and at the two week follow up visits, primary weight will be given to the two week follow up evaluation in determining if bioequivalence has been established." The primary endpoint in your reanalysis is the end of treatment visit clinical and mycological cure. This endpoint is not acceptable for this study and the analysis should be done using the data from these evaluations at the follow-up visit two weeks after the end of treatment.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 24 2006

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-075 APPLICANT: Altana, Inc.

DRUG PRODUCT: Econazole Nitrate Cream, 1%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Your clinical endpoint study fails to demonstrate bioequivalence between your product, Econazole Nitrate Cream, 1%, and the reference listed drug (RLD), Spectazole® (Ortho McNeil Pharmaceuticals) in the treatment of tinea pedis due to the following reasons:

1. The study report gave two definitions of Total Cure, each analyzed separately. Definition 1 is given in the protocol and is the standard definition for a primary outcome in tinea pedis studies. Total Cure is defined as those who had complete resolution on the Physician's Global Assessment plus mycological cure (negative KOH and fungal cure). The second definition expands the clinical cure to complete and excellent response on the Physician's Global Assessment. There was no explanation given to justify this change and it is not listed in the changes in the planned analyses. This definition is not accepted as a definition of cure for tinea pedis. You did summarize the results stating that when using the original definition, the study fails to show bioequivalence between test and reference, and when using the second definition, the study meets the bioequivalence criteria. This represents a post hoc change in clinical endpoints based on a failure of the data to meet the original endpoint criteria for success.

2. You outlined several changes in the planned analyses in the study report and the method for carrying forward missing values for the MITT was further clarified. You introduced the concept of invalid visits for this population, including visits outside the prescribed time window and visits after a prohibited medication was taken. In these instances, the last valid observation was carried forward. Since the MITT population was not defined by adherence to the protocol, this method is not appropriate. Only missing visit data should be substituted by carrying the last observation forward.

3. Patient number 06-002 was listed as a withdrawal because of an insufficient therapeutic response and should therefore be included in all analysis populations as a treatment failure.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research